UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,994	07/13/2001	Johannes Gerardus Kusters	2000.566 US	3816

31846 7590 12/10/2007

INTERVET INC.
PATENT DEPARTMENT
PO BOX 318
MILLSBORO, DE 19966-0318

EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
12/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/904,994	KUSTERS ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60,62-66,71 and 74-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60,62-66,71 and 74-81* is/are rejected.

7)☒ Claim(s) *62-66,75,76 and 80-84* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

New claims 60, 62-66,71,74-84 are pending.
Objections and rejections over canceled claims are rendered moot.
1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Withdrawn

2. Withdrawn, Claims 60-66 (amended to recite biological activity, 69 (canceled) rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
3.

Response to Arguments for Objections/Rejections Maintained

1. Applicant's arguments filed September 28, 2007 have been fully considered but they are not persuasive.

2. Applicant states the claims have been amended and submit the application is in condition for allowance. In light of various amendments of the claims, some of the objections and rejections have been obviated, but others will be maintained and addressed below.

3. ***Claim Rejections - 35 USC § 112 Amended*** Claims 60, 62-66,71,74-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed.

4. It is apparent to the examiner that based upon Applicant's amendments to the claims, that an effort to place the application in condition for allowance has been made.

Upon consideration of the definitions provided by the instant Specification the examiner found definitions for the instantly claimed variants directed to fragment polypeptides, that need not

share 94% identity over the ---- full length of nucleotides 206-2603----- of SEQ ID NO 1. (see paragraphs [14, 25,30,38-39,89]. The instantly claimed variants may be any fragment of the recited SEQ ID NO, and comprise additional nucleic acids or amino acids to result in a urease protein the overall size and sequence of which comprises a fragment of the overall claimed product. This combination of claim limitations defines a highly variable genus for which the instant Specification has not described. The lack of written description rejection is maintained herein for reasons of record and responses set forth herein.

5. Additionally, even though claim 1 has been amended to recite -----consisting of---- is closed language, all of the claims encompass a genus of nucleic acids, polypeptides and antibodies that bind to said polypeptides that bind to H. felis urease XY, X or Y and to the highly variable genus of products that comprise only fragments, mutant fragments and additional residues to result in coding sequence, and functional urease enzymes, this highly variable genus is still rejected under 35 USC 112, first paragraph (written descriptions) for reasons of record. Deletion of the term [variants] from the claims, or limiting the claims to variants that share 94% or more identity over the entire length of each reference SEQ ID NO may obviate this rejection.

[0014] A preferred form of this embodiment rèlates to nucleic acid sequences that encode the urease X subunit polypeptide or the urease Y subunit polypeptide and that have at least 85% homology with SEQ ID NO: 1, or parts thereof with a length of at least 40, preferably 45, more preferably 50 nucleotides encoding at least an immunogenic fragment of the urease X subunit polypeptide or the urease Y subunit polypeptide. Merely as an example: the nucleic acid sequence encoding the urease X subunit of Helicobacter felis strain CS1 starts at position 206/207/208 (GTG) (See FIG. 1a (1)) and stops at position 884/885/886 (TAA). the nucleic acid sequence encoding the urease Y subunit of Helicobacter felis strain CS1 starts at position 897/898/899 (ATG) and stops at position 2601/2602/2603 (TAG).

[0038] It will be understood that, for the particular polypeptides embraced herein, natural variations can exist between individual Helicobacter felis strains. These variations may be demonstrated by (an) amino acid difference(s) in the overall sequence or by deletions,

substitutions, insertions, inversions or additions of (an) amino acid(s) in said sequence. Amino acid substitutions which do not essentially alter biological and immunological activities, have been described, e.g. by Neurath et al in "The Proteins" Academic Press New York (1979). Amino acid replacements between related amino acids or replacements which have occurred frequently in evolution are, inter alia, Ser/Ala, Ser/Gly, Asp/Gly, Asp/Asn, Ile/Val (see Dayhof, M. D., Atlas of protein sequence and structure, Nat. Biomed. Res. Found., Washington D.C., 1978, vol. 5, suppl. 3). Other amino acid substitutions include Asp/Glu, Thr/Ser, Ala/Gly, Ala/Thr, Ser/Asn, Ala/Val, Thr/Phe, Ala/Pro, Lys/Arg, Leu/Ile, Leu/Val and Ala/Glu. Based on this information, Lipman and Pearson developed a method for rapid and sensitive protein comparison (Science, 227, 1435-1441, 1985) and determining the functional similarity between homologous proteins. Such amino acid substitutions of the exemplary embodiments of this invention, as well as variations having deletions and/or insertions are within the scope of the invention as long as the resulting polypeptides retain their immunoreactivity. Thus, variations not essentially influencing the immunogenicity of the polypeptide compared to the wild type polypeptide as depicted in SEQ ID NO: 2 or 3 are considered to fall within the scope of the invention. Those variations in the amino acid sequence of a certain structural subunit X or Y according to the invention that still provide a polypeptide capable of inducing an immune response against infection with H. felis or at least against the clinical manifestations of the infection are considered as "not essentially influencing the immunogenicity".

[0039] When a polypeptide is used for e.g. vaccination purposes or for raising antibodies, it is however not necessary to use the whole polypeptide. It is also possible to use a fragment of that polypeptide that is capable, as such or coupled to a carrier such as e.g. KLH, of inducing an immune response against that polypeptide, a so-called immunogenic fragment. An "immunogenic fragment" is understood to be a fragment of the full-length polypeptide of the structural subunit X or Y, that still has retained its capability to induce an immune response in the host, i.e. comprises a B- or T-cell epitope. At this moment, a variety of techniques is available to easily identify DNA fragments encoding antigenic fragments (determinants). The method described by Geysen et al (Patent Application WO 84/03564, Patent Application WO

86/06487, U.S. Pat. No. 4,833,092, Proc. Natl Acad. Sci. 81: 3998-4002 (1984), J. Imm. Meth. 102, 259-274 (1987), the so-called PEPSCAN method is an easy to perform, quick and well-established method for the detection of epitopes; the immunologically important regions of the polypeptide. The method is used world-wide and as such well-known to man skilled in the art. This (empirical) method is especially suitable for the detection of B-cell epitopes. Also, given the sequence of the gene encoding any protein, computer algorithms are able to designate specific polypeptide fragments as the immunologically important epitopes on the basis of their sequential and/or structural agreement with epitopes that are now known. The determination of these regions is based on a combination of the hydrophilicity criteria according to Hopp and Woods (Proc. Natl. Acad. Sci. 78: 38248-3828 (1981)), and the secondary structure aspects according to Chou and Fasman (Advances in Enzymology 47: 45-148 (1987) and U.S. Pat. No. 4,554,101). T-cell epitopes can likewise be predicted from the sequence by computer with the aid of Berzofsky's amphiphilicity criterion (Science 235, 1059-1062 (1987) and U.S. patent application NTIS U.S. Ser. No. 07/005,885). A condensed overview is found in: Shan Lu on common principles: Tibtech 9: 238-242 (1991), Good et al on Malaria epitopes; Science 235: 1059-1062 (1987), Lu for a review; Vaccine 10: 3-7 (1992), Berzowsky for HIV-epitopes; The FASEB Journal 5:2412-2418 (1991).

1. While specific species defined by specific nucleic acid sequences and complete amino acid sequences shown in Figure 1a have been disclosed, what the claimed variant nucleic acid molecules and polypeptides are, and what epitopes the antibodies bind on the variant polypeptides are has not been described..

Applicant also broadly describes the invention as embracing any substitution, insertion or deletion of amino acids throughout the entire stretch of nucleotides or amino acids found in the reference sequence by use of language in which only a "part" or "fragment" of the reference sequence is required, but the final relative molecular weight of the resultant protein is far larger than the region that can be selected from the reference proteins. None of the proteins that comprise any antigenic region of the recited sequence and reacts with an Helicobacter felis urease antibody, but differs by any number of amino acids, and has a sequence not represented

by the sequences of SEQ ID NO 1, 2 or 3 and, encode or comprise amino acid sequences that do not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The claimed nucleic acids and polypeptides that comprise sequences other than those set forth in Figure 1a, SEQ ID NO 1, 2 or 3, and do not evidence at least 95% identity to SEQ ID NO 1, 2 or 3 and also have enzymatic activity to catalyze the hydrolysis of urea have not been described. The specification does not provide original descriptive support for what the additional amino acid sequences are, that are in association with any number of parts, fragments or regions selected from each of the recited Helicobacter sequences.

The skilled artisan cannot envision all the contemplated nucleic acid molecules or polypeptides/proteins that encode or comprise any amino acid antigenic sequence region of Helicobacter felis ureaseXY. The detailed chemical structure of the claimed genus of proteins has not been described and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. A method of screening for antigenic immunoreactivity is not a method of making a protein, the product itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. . Thus, the written description of the instant specification does not provide for "comprising" language. Therefore, only isolated nucleic acid molecules and polypeptides of SEQ ID Nos 1, 2 and 3 and those shown in Figure 1a have been described but not the full breadth of the claim meets the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is serviceable from its enablement provision. (See page 1115.)

Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999. The rejection is maintained for reasons of record and responses set forth herein. This rejection could be partially obviated by amending the claims to recite---------95% identical----- and ----having catalyzing the hydrolysis of urea--------; or an equivalent phrase.

6. ***Maintained Claim Rejections - 35 USC § 102 Maintained.*** The rejection of claims 75 and 80 under 35 U.S.C. 102(b) as being anticipated by Gootz et al (1994) as is herein partially maintained because the antibodies produced by Gootz et al comprised antibodies directed to the claimed polypeptides and variants thereof.

7. Absent evidence to the contrary, the antibodies of Gootz et al inherently are the antibodies, now claimed in light of the fact that Gootz et al produced the claimed and disclosed polypeptide, coding nucleic acid and antibodies by a different process to obtain the same or equivalent products. Gootz et al chose H. felis ATCC 49179 (see abstract), also known as CS-1, the identical strain Applicant used to determine the sequence for urease as shown in Figure 1(a), SEQ Id NO 1 and isolated and purified the Helicobacter felis urease polypeptide (see Gootz et al, page 794, col. 1, paragraph 5), showed antibody compositions immunoreactive with the polypeptides (see Gootz et al, page 794, col. 2, paragraph 4, and Figure 3, page 795) and isolated the genes for H. felis urease in genomic blots of H.felis ATCC 49179 (see Figure 4), thus isolating the nucleic acid coding sequences for the H. felis urease polypeptides of CS-1.

8. While Gootz et al do not disclose the amino acid sequence, of the H. felis polypeptide for the H.felis CS-1 urease, by all comparable data the polypeptide to which the antibodies immunoreact are the same or equivalent compositions now claimed produced by a different

process, but obtained from the identical Helicobacter felis source as Applicants. The amino acid sequence and nucleic acid sequence of a polypeptide and nucleotide molecule, respectively, are descriptors of inherent structural residues of the polypeptide and DNA of Gootz et al. Discovery of a new descriptor of an already known product does not define a novel or unobvious product.

Gootz et al still inherently anticipates the instantly claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 64-66 are directed to non-statutory subject matter in light of Applicant's definition in [0029] "the technique of in vivo homologous recombination, well-known in the art, can be used to introduce a recombinant nucleic acid sequence into the genome of a bacterium, parasite or virus of choice, capable of inducing expression of the inserted nucleic acid sequence according to the invention **in the host animal**", which describes the invention to include animals with recombinant host cells that express the heterologous

recombinant nucleic acid sequences. This reads on host cells in humans; the claimed invention is directed to non-statutory subject matter. The claims should be amended to recite ---An isolated host cell------.

Claim Objections

11. Claims 62-66, 75-76 and 80-81 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 62-66, 75-76 and 80-81 are objected to for broadening the scope of the claim(s) from which they depend. Each independent claim encompasses variants of a specific % identity to a reference SEQ ID NO, but the dependent claims, claim variants of the already claimed variants and are therefore not further limiting of the claim(s) from which they depend as the variants of the variants need not evidence any specific % identity but may have any percent identity with the reference SEQ ID NO, and therefore a clearly broader in scope than the claim(s) from which they depend.

Allowable Subject Matter

12. Claims 82-84 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

a. This is a non-final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vgp
December 1, 2007

MARK NAVARRO
PRIMARY EXAMINER

09/904,994 [0039] When a polypeptide is used for e.g. vaccination purposes or for raising antibodies, it is however **not necessary to use the whole polypeptide**. It is also possible to use a fragment of that polypeptide that is capable, as such or coupled to a carrier such as e.g. KLH, of inducing an immune response against that polypeptide, a so-called immunogenic fragment. An "immunogenic fragment" is understood to be a fragment of the full-length polypeptide of the structural subunit X or Y, that still has retained its capability to induce an immune response in the host, i.e. comprises a B- or T-cell epitope. At this moment, a variety of techniques is available to easily identify DNA fragments encoding antigenic fragments (determinants). The method described by Geysen et al (Patent Application WO 84/03564, Patent Application WO 86/06487, U.S. Pat. No. 4,833,092, Proc. Natl Acad. Sci. 81: 3998-4002 (1984), J. Imm. Meth. 102, 259-274 (1987), the so-called PEPSCAN method is an easy to perform, quick and well-established method for the detection of epitopes; the immunologically important regions of the polypeptide. The method is used world-wide and as such well-known to man skilled in the art. This (empirical) method is especially suitable for the detection of B-cell epitopes. Also, given the sequence of the gene encoding any protein, computer algorithms are able to designate specific **polypeptide fragments** as the immunologically important epitopes on the basis of their sequential and/or structural agreement with epitopes that are now known. The determination of these regions is based on a combination of the hydrophilicity criteria according to Hopp and Woods (Proc. Natl. Acad. Sci. 78: 38248-3828 (1981)), and the secondary structure aspects according to Chou and Fasman (Advances in Enzymology 47: 45-148 (1987) and U.S. Pat. No. 4,554,101). T-cell epitopes can likewise be predicted from the sequence by computer with the aid of Berzofsky's amphiphilicity criterion (Science 235, 1059-1062 (1987) and U.S. patent application NTIS U.S. Ser. No. 07/005,885). A condensed overview is found in: Shan Lu on common principles: Tibtech 9: 238-242 (1991), Good et al on Malaria epitopes; Science 235: 1059-1062 (1987), Lu for a review; Vaccine 10: 3-7 (1992), Berzowsky for HIV-epitopes; The FASEB Journal 5:2412-2418 (1991).

[0014] A preferred form of this embodiment relates to nucleic acid sequences that encode the urease X subunit polypeptide or the urease Y subunit polypeptide and that have at least 85% homology with SEQ ID NO: 1, or parts thereof with a length of at least 40, preferably 45, more preferably 50 nucleotides encoding at least an immunogenic fragment of the urease X subunit polypeptide or the urease Y subunit polypeptide. Merely as an example: the nucleic acid sequence encoding the urease X subunit of Helicobacter felis strain CS1 starts at position 206/207/208 (GTG) (See FIG. 1a (1)) and stops at position 884/885/886 (TAA). the nucleic acid sequence encoding the urease Y subunit of Helicobacter felis strain CS1 starts at position 897/898/899 (ATG) and stops at position 2601/2602/2603 (TAG).